# PATENT COOPERATION TREATY

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# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference 00931/1 | **FOR FURTHER ACTION** See Form PCT/IPEA/416 | |
|---|---|---|
| International application No. PCT/IB2004/004203 | International filing date *(day/month/year)* 13.12.2004 | Priority date *(day/month/year)* 24.12.2003 |
| International Patent Classification (IPC) or national classification and IPC A61K31/42, C07D261/08, C07C311/51, A61P25/04 | | |
| Applicant PHARMACIA CORPORATION et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☒ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☒ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 03.06.2005 | 30.08.2005 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Cortés, J Telephone No. +49 89 2399-8206 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/004203

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

| | |
|---|---|
| **Description, Pages** | |
| 1-28 | as originally filed |
| **Claims, Numbers** | |
| 1-13 | received on 01.07.2005 with letter of 29.06.2005 |
| **Drawings, Sheets** | |
| 1/11-11/11 | as originally filed |

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 13

because:

☒ the said international application, or the said claims Nos. 13 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

## Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   **see separate sheet**

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

## Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | |
| | No: | Claims | 1-13 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-13 |
| Industrial applicability (IA) | Yes: | Claims | 1-12 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/004203

## Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   **see separate sheet**

**Re Item I**

**Basis of the opinion**

With letter of 29.06.2005 the Applicant has filed an ameded claim 7 and deleted previous claim 10. In amended claim 7 the Applicant has deleted the possibility of n=0 when M is K+. Parecoxib potassium salts are not longer claimed.

This amendment is in line with 70.2(c) PCT, since they do not extent beyond the content of the application as originally filed.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 13 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion with regard to the industrial applicability will be formulated for this claim (Article 34(4)(a)(i) PCT).

**Re Item IV**

**Lack of unity of invention**

Since parecoxib salts are already known from D1 and D2, the claimed parecoxib magnesium, calcium and zinc salts each represent a separate group of inventions.

These groups of inventions are not linked by a common inventive concept. The present application therefore lacks unity of invention according to Rule 13.1 PCT (see also chapter III-7 PCT Guidelines).

However, all three groups of inventions have been searched and examined.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The following documents have been cited in the International Search Report:

D1: US-A-5 932 598 (SEARLE) 3 August 1999 (1999-08-03)
D2: WO 03/078408 A (PHARMACIA) 25 September 2003 (2003-09-25)

Novelty (Article 33(2) PCT)

Parecoxib magnesium, calcium and zinc salts have been generically disclosed in D1 (D1: e.g. column 18, lines 20 and 21). The present generic groups of claims 1 and 7 are not a novel selection of D1, since they only represent further embodiments of the generic disclosure of D1.

Since parecoxib potassium salts have been deleted from the current claim set, claim 7 is now novel in view of D1.

D2 discloses a crystalline form of parecoxib sodium salt.

If the current claim set was directed to new individual magnesium, calcium and zinc parecoxib salts, these specific salts would be novel. The currently claimed generic groups, however, are not.

Inventive Step (Article 33(3) PCT)

D1 discloses generically parecoxib magnesium, calcium and zinc salts and can be regarded as the closest prior art.

The problem of the invention was the provision of new pharmaceutical forms of parecoxib.

Since the present solution of this problem has already been disclosed in D1, the present application lacks an inventive step.

An inventive step could be acknowledged to a set of new individual parecoxib salts if it was shown that these salts have improved properties when compared to the already known potassium salts (D1: e.g. claim 16).

**Re Item VI**
**Certain documents cited**

Reference is made to the following P-documents:

D3: WO 2004/047815 A (PHARMACIA) 10 June 2004 (2004-06-10)
D4: WO 2004/002533 A (PHARMACIA) 8 January 2004 (2004-01-08)

The priority documents pertaining to the present application were not available at the time of establishing this report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the P-documents cited in the international search report could become relevant to asses whether the present claims satisfy the criteria set forth in Article 33(1) PCT.

WHAT IS CLAIMED IS:

1. A compound having the structure $MgX^1X^2$, wherein $X^1$ is parecoxib anion and $X^2$ is selected from the group consisting of parecoxib anion, chloride, bromide, sulfate, phosphate, nitrate, acetate, propionate, succinate, glycolate, stearate, lactate, malate, tartrate, citrate, ascorbate, glutamate, benzoate, salicylate, methanesulfonate, and toluenesulfonate.

2. The compound of Claim 1 substantially in the form of magnesium diparecoxib.

3. The compound of Claim 2 wherein the molar ratio of parecoxib anion to $Mg^{2+}$ is at least about 1.5 and equal to or less than about 2.5.

4. The compound of Claim 3 in the form of a crystal.

5. The compound of Claim 4 wherein the crystals have an average particle size of less than about 20 $\mu$m as determined by a Horiba Particle Sizer.

6. The compound of Claim 4 wherein the crystal has a surface to volume ratio less than about 12 $\mu m^{-1}$.

7. A compound having the structure $MX^1X^2$ wherein:
M is a metal cation selected from the group consisting of $Ca^{2+}$ and $Zn^{2+}$;
$X^1$ is parecoxib anion; and
$X^2$ is selected from the group consisting of parecoxib anion and another pharmaceutically acceptable anion.

8. A pharmaceutical composition comprising the compound of Claim 3 or Claim 7 and at least one excipient.

9. The composition of Claim 8 wherein the excipient comprises at least one agent selected from the group consisting of an anti-oxidant, a preservative, and a moldable agent.

10. The composition of Claim 8 in a form selected from the group consisting of a pill, a tablet, a capsule, a solution, and a suspension.

11. The composition of Claim 8 suitable for injection into at least one parenteral site selected from the group of sites consisting of intradermal, intramuscular, intraarticular, intraperitoneal, intralymphoid, subcutaneous, and subdural.

12. The composition of Claim 8 wherein, upon injection into the at least one parenteral site, the dosage form provides at least one of:

(a) a therapeutic level of valdecoxib within about 5 hours after injection;

(b) a therapeutic level of valdecoxib for at least about 3 days after injection; and/or

(c) a time to reach one half maximum blood serum concentration of valdecoxib not greater than about 10 hours after injection.

13. A method for providing a long-acting selective COX-2 inhibitory effect comprising injecting into a subject an amount of the composition of Claim 8 sufficient to produce said long acting selective COX-2 inhibitory effect.